DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 19 2004

SP 04P-0136/CP1

Intervet, Inc.
Attention: S. Lee Whaley, MS
Manager, Regulatory Affairs - Pharmaceuticals
405 State Street
P.O. Box 318
Millsboro, DE 19966-9906

Dear Mr. Whaley:

We refer to your Suitability Petition filed March 18, 2004, in which you requested permission to submit an abbreviated new animal drug application (ANADA) for a generic product with a change in strength from that of an approved new animal drug. The proposed pioneer product is Schering-Plough Animal Health's Nuflor® (florfenicol) Injectable Solution which is intended for use in cattle excluding veal calves and female dairy cattle 20 months of age or older (NADA 141-063).

Your proposed product differs from the pioneer product in strength. The proposed generic product is a liquid solution, which can be administered intramuscularly or subcutaneously, as is the pioneer. The proposed generic product is intended to deliver the same amount of active ingredient per pound of body weight, and is intended for individual animal treatment, as is the pioneer.

Change in strength is one of the five variances in the pioneer product which can be considered through a Suitability Petition under section 512(n)(3) of the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended. We are required to approve the petition unless we determine that investigations must be conducted to establish the safety and effectiveness of the proposed generic product.

Your Suitability Petition is approved. Approval of the Suitability Petition does not alter the requirements for approval of the ANADA, nor assure approval of the ANADA. Please include a copy of this letter in your generic application.

An *in vivo* bioequivalence study to demonstrate bioequivalence between the pioneer and the generic products will be required. We recommend that you submit protocols for our evaluation before initiating any studies.

2004P-0136 PAV 1

DOCKETS LOG

Report run on March 19, 2004 6:27 PM ALL DATES

TITLE: ANADA SUITABILITY PETITION FOR FLORFENICOL INJECTABLE SOLUTION Docket Number: 2004P-0136
ACTION OFFICE: HFV-100 Other ID's:

Document #	Received Date	Filed Date	Submitter Code	Submitter	FR Date	FR Page	Comment Date	Volume	Remarks
CP1	03/18/2004	03/18/2004	Private Industry	Intervet, Inc. Signature: Carl K. Johnson, AM, DVM				1	
ACK1	03/18/2004	03/18/2004	Federal Government	HFA-035 to Intervet, Inc. Signature: Gloria Ortega				1	

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

March 18, 2004

Carl K. Johnson, AM, DVM
Intervet, Inc.
405 State Street
P.O. Box 318
Millsboro, Delaware 19966-9906

Dear Dr. Johnson:

Your petition requesting the Food and Drug Administration to permit the filing of an abbreviated new animal drug application (ANADA) for Florfenicol Injectable Solution, was received by this office on 03/18/2004. It was assigned docket number 2004P-0136/CP 1 and it was filed on 03/18/2004. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

Gloria Ortega

Gloria Ortega
Division of Dockets Management
Office of Management Programs
Office of Management

2004P-0136

ACK 1

000001

(302) 934-4385

16 March 2004

Dr. Lonnie Luther, Staff Chief (HFV-102)
C/O: Dockets Management Branch, HFA-305
Room 1061
5630 Fishers Lane
Food and Drug Administration
Rockville, MD 20852

RE: SUITABILITY PETITION FOR REVIEW AND ACTION – FLORFENICOL INJECTABLE SOLUTION

Dear Dr. Luther:

Please find enclosed a suitability petition for Agency review and action. Intervet Inc. is requesting permission to file an abbreviated new animal drug application (ANADA) for a generic florfenicol injectable solution that differs from the pioneer product (Nuflor®; NADA 141-063) in strength (i.e., concentration) of the active ingredient.

Your timely review of the enclosed petition will be greatly appreciated.

Please feel free to call (302-934-4385) or e-mail (lee.whaley@intervet.com) me should you have any questions or if I can be of assistance.

Sincerely,

S. Lee Whaley, MS
Manager, Regulatory Affairs – Pharmaceuticals
Intervet Inc.

Enclosure

2004P-0136 CP1

Suitability Petition

Intervet Inc.
Florfenicol Injectable Solution for Cattle
16 March 2004

The undersigned submits this petition under Section 512(n)(3) of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to permit the filing of an application for a generic florfenicol injectable solution formulation that differs from the pioneer product (Nuflor®; NADA 141-063) in strength of the active ingredient in the proposed drug product.

Action Requested

We are requesting that the Commissioner permit the filing of an Abbreviated New Animal Drug Application (ANADA) for an injectable florfenicol solution for cattle (trade name to be determined) that differs in strength from the pioneer product. The ANADA will include a bioequivalence study. Our proposed product differs from the pioneer product as follows:

Pioneer Product

Trade name

Nuflor® Injectable Solution (NADA 141-063)

Strength

30% florfenicol (wt/vol). Each milliliter contains 300 mg florfenicol.

Sponsor

Schering-Plough Animal Health Corporation.

Dosage

Nuflor injectable solution should be administered by intramuscular injection to cattle at a dose of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, Nuflor injectable solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs).

Proposed Drug Product

Trade name

To be selected

Strength

45% florfenicol (wt/vol). Each milliliter contains 450 mg florfenicol.

Sponsor

Intervet Inc.

Dosage

The florfenicol injectable solution should be administered by intramuscular injection to cattle at a dose of 20 mg/kg body weight (2 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, the injectable solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (4 mL/100 lbs).

Statement of Grounds

The proposed generic product contains the same active ingredient and will be labeled with the same indications, recommended dose rates, precautions and warnings as the approved pioneer product. The route of administration (intramuscular or subcutaneous injection) and the dosage form (injectable solution) are the same.

An injectable florfenicol solution formulation that has a greater strength of florfenicol than the pioneer product will be successful in administering the required amount of the antibiotic in a reduced volume, potentially decreasing the number of injection sites. While this product has a change in strength of the active ingredient compared to the pioneer, the dose of florfenicol administered per kilogram body weight is the same as the pioneer product.

Environmental Impact

Intervet Inc. requests a categorical exclusion under 21 CFR 25.33(d)(5) from the requirements to file an environmental impact assessment, as the drug is intended for use under veterinary prescription or veterinarian's order for therapeutic use in a terrestrial species.

Economic Impact

Information pertaining to the economic impact of this petition will be submitted if requested by the Commissioner.

Differences Between Pioneer and Proposed Generic Product Labeling

The changes in the labeling noted below may not be placed in the same areas as they are located on the pioneer product. The changes noted will be reflected in the proposed drug product's labeling in an appropriate manner so that it is clear and readily understood by the end-user. Please see the attached proposed labeling.

References to "Nuflor® Injectable Solution" will be changed to "florfenicol" or to the new brand name as appropriate throughout the labeling.

The Nuflor name and logo will be removed and replaced with the new brand name and logo throughout the labeling.

References to "300 mg/mL" will be changed to indicate the product contains "450 mg/mL" florfenicol.

The product number will be changed.

The NADA number will be changed.

The sponsor information will be changed.

Under Description:

Changes in the formulation constituents of the pioneer will be appropriately reflected in the generic product labeling. Each milliliter will contain "450 mg of florfenicol".

Under Dosage and Administration:

The text of this section of the label will be changed to reflect the 450 mg/mL formulation and 2 mL/100 lbs or 4 mL/100 lbs dosage, as appropriate.

Certification

Intervet Inc. certifies that this suitability petition contains all information known to them that is unfavorable to the petition.

Carl K. Johnson, AM, DVM
Director, Product Development and
Regulatory Affairs – Pharmaceuticals

16 Mar 04
Date

Proposed Generic Labeling

PROPOSED GENERIC PRODUCT LABELING

NADA No. *XXX-XXX*, Approved by FDA *(NOTE: NADA # to be determined)*
Intervet Inc.

***XXX* mL Multiple-Dose Vial** *[NOTE: Vial size(s) to be determined]*

***"TRADENAME"* INJECTABLE SOLUTION 450 mg/ml**
(Florfenicol)

For intramuscular and subcutaneous use in cattle only.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: *"TRADENAME"* Injectable is a solution of the synthetic antibiotic florfenicol. Each millimeter of sterile *"TRADENAME"* Injectable Solution contains 450 mg of florfenicol *(NOTE: Excipients to be determined)*.

CLINICAL PHARMACOLOGY: The pharmacokinetic disposition of florfenicol injectable solution was evaluated in feeder calves following single intramuscular administration at the recommended dose of 20 mg/kg. Florfenicol injectable solution was also administered intravenously to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability[1] (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C_{MAX} (µg/mL)	3.07*	1.43 - 5.60
T_{MAX} (hr)	3.33	0.75 - 8.00
T½, (hr)	18.3**	8.30 - 44.0
AUC (µg•min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd_{ss} (L/kg)***	0.77	0.68 - 0.85
Cl_t (mL/min/kg)***	3.75	3.17 - 4.31

* harmonic mean
** mean value
*** following I.V. administration
C_{MAX} Maximum serum concentration
T_{MAX} Time at which C_{MAX} is observed
T½ Biological half-life
AUC Area under the curve
Vd_{ss} Volume of distribution at steady state
Cl_t Total body clearance

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively.

MICROBIOLOGY: Florfenicol is a synthetic, broad-spectrum antibiotic active against many gram-negative and gram-positive bacteria isolated from domestic animals. It is primarily bacteriostatic and acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. *In vitro* and *in vivo* activity has been demonstrated against commonly isolated bacterial pathogens involved in bovine respiratory disease (BRD), including *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus*, as well as against commonly isolated bacterial pathogens involved in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

TABLE 2. MIC Values* of Florfenicol Against Bacterial Isolates From Natural Infection of Cattle

Organism	Isolate Numbers	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)
Pasteurella haemolytica	398	0.50	1.00
Pasteurella multocida	350	0.50	0.50
Haemophilus somnus	66	0.25	0.50
Fusobacterium necrophorum	33	0.25	0.25
Bacteroides melaninogenicus	20	0.25	0.25

* The correlation between the *in vitro* susceptibility data (MIC values) and clinical response has not been determined.

** The minimum inhibitory concentration for 50% and 90% of the isolates.

INDICATIONS: *"TRADENAME"* Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus*, and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus*.

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call *XXX-XXX-XXXX*. *(NOTE: Phone number to be determined.)*

CAUTION: Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

ADVERSE EFFECTS: Inappetance, decreased water consumption, or diarrhea may occur transiently following treatment.

TOXICOLOGY: A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased bodyweight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group.

Decreased feed and water consumption, bodyweight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.

A 43-day controlled study was conducted in healthy cattle to evaluate effects of florfenicol injectable solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, florfenicol injectable solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

DOSAGE AND ADMINISTRATION: For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): *"TRADENAME"* Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (2 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, *"TRADENAME"* Injectable Solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (4 mL/100 lbs). Do not administer more than 10 mL at each site. **The injection should be given only in the neck.**

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high-risk of developing BRD: *"TRADENAME"* Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (4 mL/100 lbs). Do not administer more than 10 mL at each site. **The injection should be given only in the neck.**

"TRADENAME" Dosage Guide		
ANIMAL WEIGHT (lbs)	IM *"TRADENAME"* Dosage 2.0 mL/100 lb Body Weight (mL)	SC *"TRADENAME"* Dosage 4.0 mL/100 lb Body Weight (mL)
100	2.0	4.0
200	4.0	8.0
300	6.0	12.0
400	8.0	16.0
500	10.0	20.0
600	12.0	24.0
700	14.0	28.0
800	16.0	32.0
900	18.0	36.0
1000	20.0	40.0

Recommended Injection Location *(NOTE: Picture of cow and syringe showing recommended injection location will be inserted as pictured on pioneer label.)*

Do not inject more than 10 mL per injection site.

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

STORAGE CONDITIONS: Store between 2°-30°C (36°-86°F). Refrigeration is not required. The solution is *XXXXX* to *XXXXX* colored (*Note: Color to be determined*). Color does not affect potency.

HOW SUPPLIED: *"TRADENAME"* Injectable Solution is packaged in *XXX* mL glass sterile multiple-dose vials. *[Note: Vial size(s) to be determined.]*

REFERENCE: 1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. *J Vet Pharmacol Therap.* 1994; 17:253-258.

intervet

Distributed by:
INTERVET INC.
Millsboro, DE 19966
Made in *"XXX" (Note: to be determined)*

Pioneer Labeling

F-19659143

PRODUCT INFORMATION

NADA #141-063, Approved by FDA.

Nuflor®
(FLORFENICOL)

Injectable Solution
300 mg/mL

For Intramuscular and Subcutaneous Use in Cattle Only.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: NUFLOR Injectable is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile NUFLOR Injectable Solution contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol q.s.

CLINICAL PHARMACOLOGY: The pharmacokinetic disposition of NUFLOR Injectable Solution was evaluated in feeder calves following single intramuscular administration at the recommended dose of 20 mg/kg. NUFLOR Injectable Solution was also administered intravenously to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability[1] (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol Following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C_{MAX} (μg/mL)	3.07*	1.43 - 5.60
T_{MAX} (hr)	3.33	0.75 - 8.00
$T_{½}$ (hr)	18.3**	8.30 - 44.0
AUC (μg•min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd_{SS} (L/kg)***	0.77	0.68 - 0.85
Cl_T (mL/min/kg)***	3.75	3.17 - 4.31

* harmonic mean
** mean value
*** following I.V. administration
C_{MAX} Maximum serum concentration
T_{MAX} Time at which C_{MAX} is observed
$T_{½}$ Biological half-life
AUC Area under the curve
Vd_{SS} Volume of distribution at steady state
Cl_T Total body clearance

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 μg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 μg/mL, respectively.

MICROBIOLOGY: Florfenicol is a synthetic, broad-spectrum antibiotic active against many gram-negative and gram-positive bacteria isolated from domestic animals. It is primarily bacteriostatic and acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. *In vitro* and *in vivo* activity has been demonstrated against commonly isolated bacterial pathogens involved in bovine respiratory disease (BRD) including *Pasteurella haemolytica, Pasteurella multocida,* and *Haemophilus somnus,* as well as against commonly isolated bacterial pathogens involved in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

TABLE 2. MIC Values* of Florfenicol Against Bacterial Isolates From Natural Infection of Cattle

Organism	Isolate Numbers	MIC_{50}** (μg/mL)	MIC_{90}** (μg/mL)
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Haemophilus somnus	66	0.25	0.50
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Bacteroides melaninogenicus	20	0.25	0.25

*The correlation between the *in vitro* susceptibility data (MIC values) and clinical response has not been determined.
**The minimum inhibitory concentration for 50% and 90% of the isolates.

INDICATIONS: NUFLOR Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella multocida,* and *Haemophilus somnus,* and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.* Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica, Pasteurella multocida,* and *Haemophilus somnus.*

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call 1-800-211-3573.

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CAUTION: Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

ADVERSE EFFECTS: Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

TOXICOLOGY: A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased bodyweight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.

A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group. Decreased feed and water consumption, bodyweight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.

A 43-day controlled study was conducted in healthy cattle to evaluate effects of NUFLOR Injectable Solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, NUFLOR Injectable Solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

DOSAGE AND ADMINISTRATION: For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): NUFLOR Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, NUFLOR Injectable Solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. **The injection should be given only in the neck.**

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high-risk of developing BRD: Nuflor Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. **The injection should be given only in the neck.**

NUFLOR DOSAGE GUIDE		
ANIMAL WEIGHT (lbs)	IM NUFLOR DOSAGE 3.0 mL/100 lb Body Weight (mL)	SC NUFLOR DOSAGE 6.0 mL/100 lb Body Weight (mL)
100	3.0	6.0
200	6.0	12.0
300	9.0	18.0
400	12.0	24.0
500	15.0	30.0
600	18.0	36.0
700	21.0	42.0
800	24.0	48.0
900	27.0	54.0
1000	30.0	60.0

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

STORAGE CONDITIONS: Store between 2°-30°C (36°-86°F). Refrigeration is not required. The solution is light yellow to straw colored. Color does not affect potency.

HOW SUPPLIED: NUFLOR Injectable Solution is packaged in 100 mL (NDC 0061-1116-04), 250 mL (NDC 0061-1116-05), and 500 mL (NDC 0061-1116-06) glass sterile multiple-dose vials.

REFERENCE: 1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. *J Vet Pharmacol Therap.* 1994; 17:253-258.

January 1999

19659143 Rev 1/99

IMPORTANT: See Product information sheet for complete directions and warnings before using.

DESCRIPTION: Each milliliter contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 130 mg propylene glycol, and polyethylene glycol q.s.

DOSAGE AND ADMINISTRATION

For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): NUFLOR Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, NUFLOR Injectable Solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

For control of respiratory disease in cattle at high-risk of developing BRD: Nuflor Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 36 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established for preruminating calves. Do not use in calves to be processed for veal.

CAUTION: Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

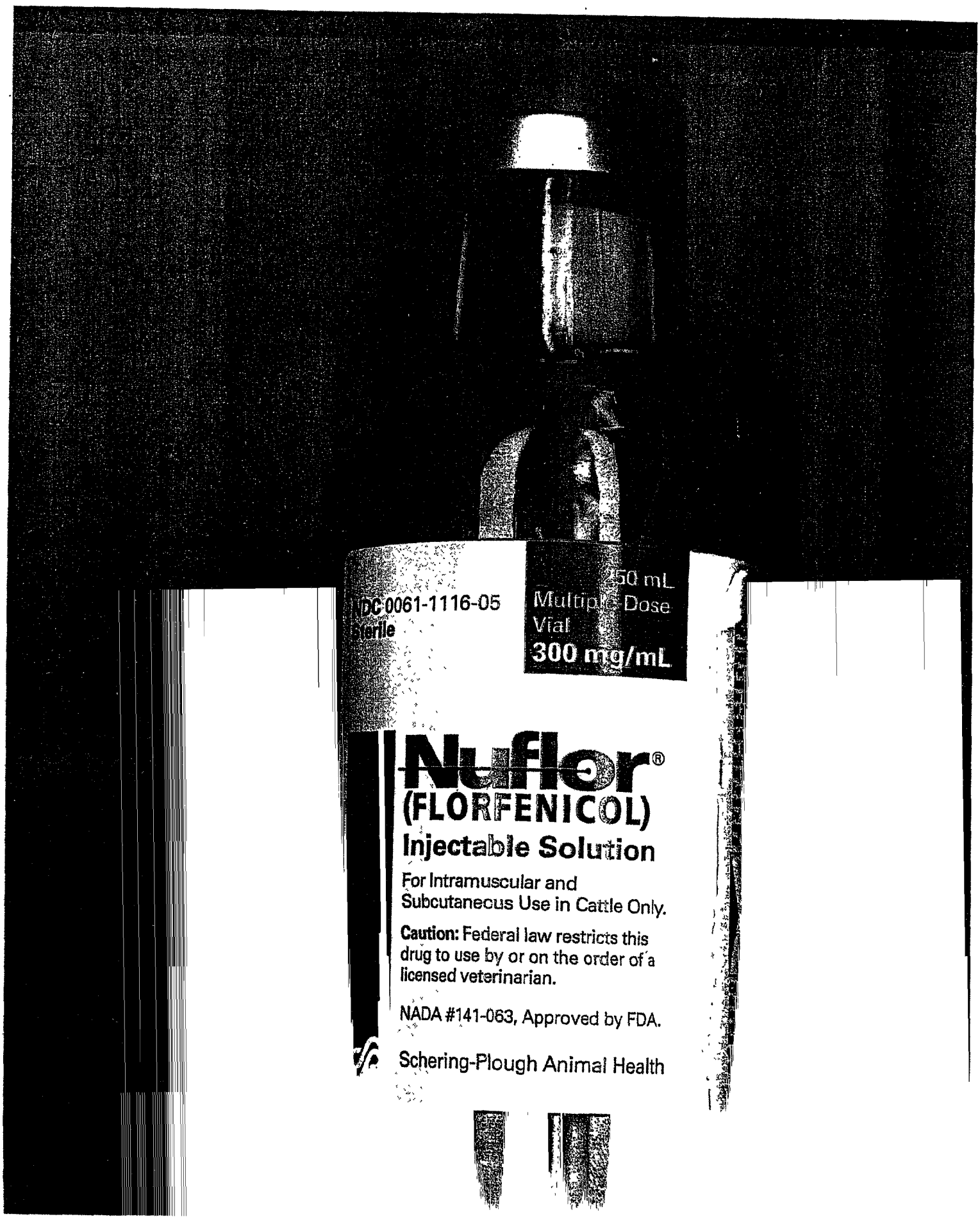
STORAGE CONDITIONS: Store between 2°-30°C (36°-86°F).

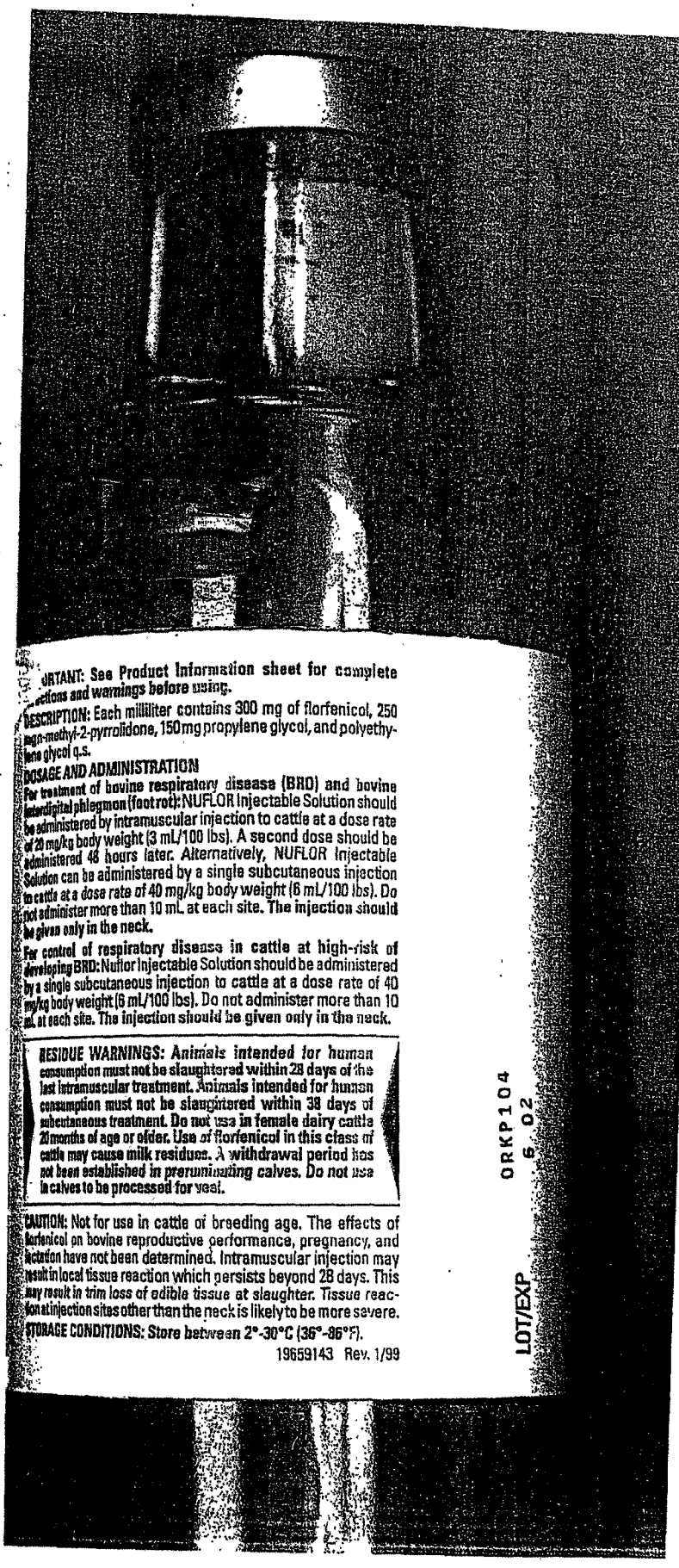
19659143 Rev 1/99

NADA 141-029, Approved by FDA

NDC 0061-1116-04

00611 11605 4


NDC 0061-1116-05
Sterile
250 mL
Multiple Dose
Vial
300 mg/mL
Nuflor®
(FLORFENICOL)
Injectable Solution
For Intramuscular and
Subcutaneous Use in Cattle Only.
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
NADA #141-063, Approved by FDA.
Schering-Plough Animal Health



ORTANT: See Product Information sheet for complete ections and warnings before using.

DESCRIPTION: Each milliliter contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol q.s.

DOSAGE AND ADMINISTRATION

For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): NUFLOR Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, NUFLOR Injectable Solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

For control of respiratory disease in cattle at high-risk of developing BRD: Nuflor Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.

CAUTION: Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

STORAGE CONDITIONS: Store between 2°-30°C (36°-86°F).

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FDA Approved Animal Drug Products
Online Database System
Drug Product Abstract

141-063
(Rx)

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Please note that the US Code of Federal Regulations (21 CFR version April 1, 2003) is the **official** source of regulatory information concerning approved animal drug products.

Tradename(s)	Nuflor® Injectable Solution
Sponsor	Schering-Plough Animal Health Corp.
Ingredient(s)	Florfenicol
Species	Cattle, beef, excluding veal calves; Cattle, dairy, females under 20 months of age
Route(s)	Intramuscular; Subcutaneous
DoseForm(s)	Liquid (solution)
Withdrawal Time(s)	Cattle: 28 days before slaughter if given IM; 38 days if given SQ. A withdrawal time for pre-ruminating veal calves has not been established.

CFR Indications
522.955 Florfenicol solution.

Specifications:
Each milliliter of sterile solution contains 300 milligrams of florfenicol.

Conditions of use:

Cattle

Amount:
20 mg per kilogram of body weight as an intramuscular injection. A second dose should be administered 48 hours later.

Indications:
For treatment of bovine respiratory disease (BRD) associated with Mannheimia (Pasteurella) haemolytica, Pasteurella multocida, and Haemophilus somnus. For treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with Fusobacterium necrophorum and Bacteroides melaninogenicus.

Limitations:
Do not slaughter within 28 days of last intramuscular treatment or within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Amount:
40 milligrams per killogram body weight as a single subcutaneous injection.

Indications:
For control of respiratory disease in cattle at high risk of developing BRD associated with M. (Pasteurella) haemolytica, P. multocida, and H. somnus. For treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with Fusobacterium necrophorum and Bacteroides melaninogenicus.

Limitations:
Do not slaughter within 28 days of last intramuscular treatment or within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

To see the complete April 1, 2003 version of the Code of Federal Regulations go to http://www.gpo.gov/nara/cfr/index.html. Our downloaded copy of 21 CFR Part 522.955 is here.

Tolerances for Florfenicol
Cattle
a.Liver (the target tissue). The tolerance for florfenicol amine (the marker residue) is 3.7 parts per million (ppm).
b. Muscle. The tolerance for florfenicol amine (the marker residue) is 0.3 ppm.

Swine
a. Liver (the target tissue). The tolerance for parent florfenicol (the marker residue) is 2.5 ppm.
b. Muscle. The tolerance for parent florfenicol (the marker residue) is 0.2 ppm.

Acceptable Daily Intake for Florfenicol
The acceptable daily intake for total residues of florfenicol is 10 micrograms per kilogram of body weight per day.

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